APPENDIX L

PATENT
Customer No. 22,852
Attorney Docket No. 08201.0024-00000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
BROWNING et al.	Group Art Unit: 1644
Serial No.: 09/911,777	Examiner: Haddad, Maher M.
Filed: July 24, 2001	
For: BAFF, INHIBITORS THEREOF AND THEIR USE IN THE MODULATION OF B-CELL RESPONSE	

MAIL STOP AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT UNDER 37 C.F.R. § 1.116

This is a reply to the Office Action, mailed August 27, 2003.

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 3 of this paper.

Attachments to this Response include:

1. Furie et al. 2003 ACR meeting abstract;
2. Wendy et al. 2003 ACR meeting abstract;
3. Declaration of Susan Kalled under 37 C.F.R. § 1.132; and
4. Kayagaki et al. (2002) Immunity, 10:515-524.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

IN THE CLAIMS:

Claims 1-9 (canceled)

Claim 10 (currently amended): A method of inhibiting B-cell growth in an animal comprising the step of administering a therapeutically effective amount of an anti-BAFF antibody ~~specific for BAFF ligand~~ that recognizes human (SEQ ID NO:1) or murine (SEQ ID NO:2) BAFF ~~or an antigenic determinant thereof~~.

Claim 11 (currently amended): A method of inhibiting immunoglobulin production in an animal comprising the step of administering a therapeutically effective amount of an anti-BAFF antibody ~~specific for BAFF ligand~~ that recognizes human (SEQ ID NO:1) or murine (SEQ ID NO:2) BAFF ~~or an antigenic determinant thereof~~.

Claim 12 (currently amended): A method of co-inhibiting B-cell growth and immunoglobulin production in an animal comprising the step of administering a therapeutically effective amount of an anti-BAFF antibody ~~specific for BAFF ligand~~ that recognizes human (SEQ ID NO:1) or murine (SEQ ID NO:2) BAFF ~~or an antigenic determinant thereof~~.

Claim 13 (currently amended): A method of inhibiting ~~dendritic cell-induced~~ B-cell growth and maturation in an animal comprising the step of administering a therapeutically effective amount of an anti-BAFF antibody ~~specific for BAFF ligand~~ that recognizes human (SEQ ID NO:1) or murine (SEQ ID NO:2) BAFF ~~or an antigenic determinant thereof~~.

Claims 14-15 (canceled)

Claim 16 (original): The method according to claims 10-13, wherein the anti-BAFF ~~recepter~~ antibody is a monoclonal antibody.

Claims 17-50 (canceled)

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

REMARKS

Claims 10-13 and 16 have been amended with this Response as shown above. Support for the amendments can be found in the specification and claims as filed, for example, on page 7, lines 27-28; page 15, lines 23-31; page 16, lines 1-10; page 26, lines 28-31; and page 27, lines 1-21. No new matter was added.

Applicants respectfully request entry of this Amendment under 37 C.F.R. § 1.116, which places the claims in condition for allowance or in better form for appeal. The proposed amendments do not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner since all of the elements claims were either earlier claimed or inherent in the claims as examined. Applicants respectfully submit that this Amendment should allow immediate action by the Examiner.

Applicants thank the Examiner for the telephonic interview conducted on November 6, 2003. The substance of the interview is set forth in detail below.

All pending claims were discussed. The Examiner contends that mouse and human BAFF sequences provided in the specification are not sufficient to enable antibodies specific to other species. Applicants respectfully disagree. Although Applicants do not concede that the claim language violates 35 U.S.C. § 112, ¶1, in order to expedite prosecution, Applicants have agreed to amend the claims to recite "anti-BAFF antibody that recognizes human (SEQ ID NO:1) or murine (SEQ ID NO:2) BAFF." Applicants note that antibodies directed against a protein from one species may, and often do, cross-react with orthologs of that protein from other species, particularly if there is a high percent identity with a respective ortholog. Additionally,

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

antibodies against a protein typically also recognize variants of that protein, including, for example, fragments and modified sequences, so long as the antigenic determinant(s) remain(s) intact. The claims, as amended, encompass all such antibodies.

During the interview, the Examiner acknowledged that abstracts by Furie et al. and Wendy et al. (American College of Rheumatology (ACR), 67th Annual Scientific Meeting, Orlando, FL, October 23-28, 2003, Abstracts #922 and #1537, respectively) provide sufficient evidence to show that B-cell growth is inhibited by anti-BAFF ligand antibody. To complete the record, Applicants submit copies of the Furie and Wendy abstracts with this response.

The Examiner requested that Applicants provide additional evidence regarding inhibition of immunoglobulin production. Accordingly, with this response, Applicants submit the Declaration of Dr. Susan Kalled. The Declaration provides further evidence that BAFF antagonism leads to inhibition of immunoglobulin production and/or B cell growth/maturation in an animal, as claimed. Dr. Kalled and her colleagues evaluated treatment of BAFF transgenic mice with a soluble form of a BAFF receptor, BCMA (B cell maturation antigen). Dr. Kalled provides experimental evidence that total serum immunoglobulins (Ig), splenolomegaly, and the numbers of MZ and mature B cells are significantly inhibited by the treatment with the BAFF receptor. *See* ¶10. These therapeutic effects are attributed to sequestration of BAFF. *Id.* Dr. Kalled further states that administration of soluble forms of other BAFF receptors or anti-BAFF antibody that recognizes human and/or mouse BAFF is expected to reduce immunoglobulin production and B cell growth. *See* ¶11.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Additionally, Applicants submit an article by Kayagaki et al. (Immunity, 10:515-524) which demonstrates that treatment with anti-BAFF antibody is expected to reduce total Ig and autoantibody production in yet another animal model. Kayagaki evaluated treatment of NZB/WF1 mice with a soluble form of a BAFF receptor, BAFF-R-Fc (also known as BR3). Kayagaki shows that mice treated with BAFF-R-Fc exhibit a reduced proteinuria (which is indicative of immunoglobulin production) and a corresponding reduction in the anti-dsDNA autoantibody titer (Figs. 4C and 4B). Although Kayagaki did not use an anti-BAFF antibody in the study, those of skill in art would expect results with an anti-BAFF antibody to be similar due to the structural and functional similarity between BAFF-R-Fc and an anti-BAFF antibody.

In view of the foregoing amendments and remarks, Applicants believe that the claims are in condition for allowance. Should the Examiner require further clarification, the Examiner is welcome to call the undersigned at (617) 452-1650.

Please grant any extensions of time required to enter this response and charge any additional required fees to deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: January 16, 2004

By: _____
Leslie McDonell
Reg. No. 34,872

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

Search Lymphostat Search
Display As Presentations Sessions Advanced Search Browse My Itinerary

Key: ☐ Click the checkbox next to an item to add to your itinerary

Results matching the search 1-2 of 2

	Presentation	Authors	Session
1. ☐	922. Safety, Pharmacokinetic and Pharmacodynamic Results of a Phase 1 Single and Double Dose-Escalation Study of LymphoStat-B (Human Monoclonal Antibody to BLyS) in SLE Patients (Board 317)	R. Furie[1], W. Stohl[2], E. Ginzler[3], M. Becker[4], N. Mishra[5], W. Chatham[6], Joan T. Merrill[7], A. Weinstein[8], W. J. McCune[9], J. Zhong[10], W. Freimuth[10], and the LymphoStat-B Study Group. [1]North Shore Univ Hosp, Manhasset, NY; [2]USC, Los Angeles, CA; [3]SUNY Downstate, Brooklyn, NY; [4]U Chicago, Chicago, IL; [5]Wake Forest U, Winston-Salem, NC; [6]UAB, Birmingham, AL; [7]OMRF, Oklahoma City, OK; [8]Wash Hosp Ctr, Washington, DC; [9]U Michigan, Ann Arbor, MI; [10]Human Genome Sciences, Rockville, MD	ACR/ARHP Poster Session B SLE Treatment—Biologic Agents Sunday, 8:00 a.m. - 4:00 p.m. Convention Center - Hall D - E
2. ☐	1537. Effects of LymphoStat-B, a BLyS Antagonist, when Administered Intravenously to Cynomolgus Monkeys. (Board 380)	Wendy B. G. Halpern[1], Patrick Lappin[2], Thomas Zanardi[2], David M. Hilbert[1], Paul A. Moore[1], Vivian R. Albert[1], Kevin P. Baker[1]. [1]Human Genome Sciences Inc., Rockville, MD; [2]Charles River Laboratories, Sparks, NV	ACR/ARHP Poster Session C SLE—Animal Models II: B-Cells/Pathogenesis Monday, 8:00 a.m. - 4:00 p.m. Convention Center - Hall D - E

Add All Matches to My Itinerary

Page: 1

American College of Rheumatology
1800 Century Place, Suite 250
Atlanta, GA 30345
Technical support Email: support@abstractsonline.com

Safety, Pharmacokinetic and Pharmacodynamic Results of a Phase 1 Single and Double Dose-Escalation Study of LymphoStat-B (Human Monoclonal Antibody to BLyS) in SLE Patients

Category: 24 SLE—treatment: developments in the treatment of SLE

R. Furie[1], W. Stohl[2], E. Ginzler[3], M. Becker[4], N. Mishra[5], W. Chatham[6], Joan T. Merrill[7], A. Weinstein[8], W. J. McCune[9], J. Zhong[10], W. Freimuth[10], and the LymphoStat-B Study Group. [1]North Shore Univ Hosp, Manhasset, NY; [2]USC, Los Angeles, CA; [3]SUNY Downstate, Brooklyn, NY; [4]U Chicago, Chicago, IL; [5]Wake Forest U, Winston-Salem, NC; [6]UAB, Birmingham, AL; [7]OMRF, Oklahoma City, OK; [8]Wash Hosp Ctr, Washington, DC; [9]U Michigan, Ann Arbor, MI; [10]Human Genome Sciences, Rockville, MD

Presentation Number: 922

Poster Board Number: 317

Purpose: LymphoStat-B is a fully human monoclonal antibody (mAb), which inhibits soluble B-Lymphocyte Stimulator (BLyS). A randomized double-blind study evaluated the safety, tolerability, immunogenicity and pharmacology (PK) of 4 different doses (1, 4, 10, 20 mg/kg) of LymphoStat-B or placebo administered as a single IV infusion or 2 infusions 21 days apart. Subjects had stable mild to moderate SLE disease activity and were on a stable standard of care SLE treatment regimen for 2 months prior to enrollment.

Methods: Patients were followed for 84-105 days for assessment of adverse events (AEs), PK and safety plus measurement of peripheral B-cell concentrations, serologies and disease activity (SELENA SLEDAI). Data from placebo subjects (n=13) in single or double dose cohorts were pooled and compared to LymphoStat-B subjects (n=57) in each of the 4 single or double dose cohorts.

Results: Study subjects were predominantly female (91%) with an average age of 41. The mean disease duration was 8.5 years with a baseline mean SELENA SLEDAI score = 2.2. LymphoStat-B was well tolerated at all doses with no study withdrawals. The overall incidence of AEs was similar between LymphoStat-B and placebo groups. There was no increased incidence of infections in the treatment group, and none of the infections reported were attributed to study agent. Six patients experienced serious adverse events with similar frequencies observed in the placebo and treatment groups. None were deemed related to study agent. Severe (grade 3 and 4) laboratory abnormalities or AEs occurred infrequently. One patient experienced an infusion reaction at the highest single dose. One patient developed neutralizing antibodies to LymphoStat-B. Pharmacokinetics of single doses were dose-proportional. Long $t_{1/2}$ = 13-17 days, slow clearance = 4.00 ± 1.56 mL/day/kg and small Vss = 68.19 ± 20.83 mL/kg are consistent with a fully human mAb. All LymphoStat-B cohorts had significant reductions of $CD20^+$ cells (12-47%) at 1 or more visits from day 42-105 compared to placebo. Reductions in anti-dsDNA or Ig levels were observed in some LymphoStat-B cohorts compared to placebo. No change in SLE disease activity was observed over this short exposure.

Conclusions: LymphoStat-B was well tolerated in SLE patients. There was a significant reduction of peripheral B-cells by LymphoStat-B consistent with its ability to bind and inhibit the biological activity of BLyS. These results support phase II trials testing for clinical benefit in patients with SLE and other autoimmune diseases.

Effects of LymphoStat-B, a BLyS Antagonist, when Administered Intravenously to Cynomolgus Monkeys.

Category: 26 SLE—animal models

Wendy B. G. Halpern[1], Patrick Lappin[2], Thomas Zanardi[2], David M. Hilbert[1], Paul A. Moore[1], Vivian R. Albert[1], Kevin P. Baker[1]. [1]Human Genome Sciences Inc., Rockville, MD; [2]Charles River Laboratories, Sparks, NV

Presentation Number: 1537

Poster Board Number: 380

Purpose: This study was conducted to evaluate the tolerability and effects of LymphoStat-B administered over 6 months to cynomolgus monkeys. LymphoStat-B is a fully-human IgG_1 lambda antibody directed against B-lymphocyte stimulator (BLyS). BLyS is a TNF family member that supports B-lymphocyte maturation and survival and has been implicated in the pathogenesis of several autoimmune diseases. LymphoStat-B was developed to antagonize the activity of BLyS in autoimmune disease, where undesirable effects of B-lymphocyte activity may cause or contribute to disease. LymphoStat-B binds specifically and with high affinity to recombinant BLyS protein from both humans and cynomolgus monkeys, and neutralizes their bioactivity *in vitro*.

Methods: LymphoStat-B was administered intravenously every other week to 16 monkeys per group at 5, 15 or 50 mg/kg/dose. A vehicle control was administered to 12 monkeys. Pharmacodynamic study endpoints included immunophenotyping of peripheral blood and tissues (spleen and lymph node), as well as standard clinical and anatomic pathology. Pathology endpoints were evaluated after 3 and 6 months of treatment, and after an 8-month treatment free (recovery) period.

Results: LymphoStat-B was well tolerated when administered intravenously to cynomolgus monkeys at doses up to 50 mg/kg for as long as 26 weeks, with no treatment-related infections identified. As detected by flow cytometric methods, monkeys exposed to LymphoStat-B had significant decreases in peripheral blood $CD20^+$ lymphocytes (B-cells) and $CD20^+/CD21^+$ lymphocytes (mature B-cells) after 13 weeks of exposure, with concomitant decreases in spleen and lymph node B-lymphocyte representation (both $CD20^+$ and $CD20^+/CD21^+$ cells). In contrast, neither $CD3^+$ T-lymphocytes nor $CD3^+/CD14^+$ monocytes were affected by LymphoStat-B. Microscopically, monkeys treated with LymphoStat-B had mild to marked decreases in the number and size of lymphoid follicles in the white pulp of the spleen. In addition, decreased spleen weights were evident after 26 weeks of exposure in LymphoStat-B treated monkeys. Overall there was a general correlation between peripheral blood B-lymphocytes, tissue B-lymphocyte representation, spleen weights and histologic findings. Total lymphocyte counts were similar in all groups throughout the study. In this study LymphoStat-B administration did not clearly affect globulins, albumin to globulin ratio, or immunoglobulin subclasses. All findings were generally reversible within the 8 month recovery period.

Conclusions: These data confirm the specific pharmacologic activity of LymphoStat-B in reducing B-lymphocytes in the cynomolgus monkey. Furthermore, the nonclinical safety profile of LymphoStat-B in monkeys supports its clinical development as a potential therapeutic for the treatment of autoimmune disease.